PRM38

MEASUREMENT PROPERTIES OF THE SPANISH VERSION OF THE PEDIATRIC PROMIS FATIGUE ITEM BANK

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OBJECTIVES: Fatigue is common among children with chronic conditions. In order to compare results across languages, a requirement for many clinical trials, one must ensure measurement is not biased by language. This paper reports the psychometric properties of the Spanish version of the pediatric PROMIS (Patient Reported Outcomes Measurement Information System) fatigue item bank (Spanish-PedsFIB). Developed via a collaborative effort funded by the National Institutes of Health of the United States, PROMIS allows for comparisons across domains and conditions for both adults and children. **METHODS:** Data from 605 Spanish-speaking participants, recruited from a US general population panel, were analyzed. Average age was 12.3 years and 45.5% were female. Participants completed the 23-item Spanish-PedsFIB, translated from English via a rigorous methodology (2 forward translations, 1 reconciliation, 1 back-translation, review by bilingual experts, and cognitive debriefing). Psychometric analyses included confirmatory factor analysis (CFA) to evaluate unidimensionality (criteria: comparative fit index CFI > 0.95; RMSEA < 0.08, MI <10), residual correlations to evaluate local dependency (criterion: $r<0.15$), S-G^2 and S-χ^2 to evaluate item fit (criterion: $p > 0.01$). Graded Response Model as implemented in MULTILOG was used to estimate item parameters, and LORDIF (R freeware) was used to evaluate differential item functioning between the Spanish and English versions (criteria: $p<.01$). **RESULTS:** CFA results supported unidimensionality of these 23 items: CFI=0.995, RMSEA=0.056, residual correlation absolute values ranged from 0 to 0.05, and R^2 ranged from 0.69 and 0.87. One item had poor fit with $p=0.0041$ and 0.0093 for S-G^2 and S-χ^2, respectively. Six items (measuring more severe fatigue) exhibited significant DIF. Correlation between scores with and without DIF candidate items was 0.97. **CONCLUSIONS:** Excellent psychometric properties of the Spanish version of Spanish-PedsFIB were evidenced. Comparative studies can be conducted using the English and Spanish versions. Currently, more translations are in progress.

RESEARCH ON METHODS - Statistical Methods

PRM39

SURVIVAL CURVE CONVERGENCES AND CROSSING: A THREAT TO VALIDITY OF META-ANALYSIS?

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OBJECTIVES: When data from survival analysis are summarized in meta analysis, they are usually based on the number of events at the end of the study. This will bias the estimates of differences in survival unless the relative hazards are relatively constant (the proportional hazards assumption). The aim of this study was to explore this assumption by estimating the frequency of convergences and crossings of survival curves. **METHODS:** We reviewed all publications in Annals of Internal Medicine, British Medical Journal, JAMA, New England Journal of Medicine (NEJM) and The Lancet for 2007 and identified studies that included survival graphs. We extracted the following data from included studies: type of disease, type of exposure, sample size and number of events, maximum follow-up time, number and timing of survival curve convergences and crossings, and whether Cox regression and log-rank tests had been performed. **RESULTS:** Among 175 included studies, 35% had survival curve convergences and 47% crossings. 38% of the crossings occurred later than halfway through the study (40% for convergences). The proportion of crossings by type of disease was 46% for cardiovascular disease, 38% for cancer and 53% for other diseases. Among studies with survival curve crossings, Cox regression was performed in 66% and logrank-test in 70% of the studies. Only 31% of all the studies reported testing for proportional hazards when Cox regression had been employed. **CONCLUSIONS:** Survival curve convergences and crossings are common in medical research. Effectiveness estimates based on end of study results will likely be biased unless convergences and crossings are accounted for, and this bias will carry over to meta analyses of individual studies. Researchers frequently employ Cox modeling when the proportional hazard assumption is not met or use log rank tests when other test would be more appropriate.

PRM40

APPLYING STRATIFICATION ON TIME TO OVERCOME TIME-VARYING COVARIATES EFFECTS IN COX PROPORTIONAL HAZARDS MODELS

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OBJECTIVES: Cox proportional hazards models are widely used in the analysis of survival data to explain the effects of prognostic factors on survival time. The model assumes proportionality of prognostic factors over time. Prognostic factor values, however, are often not constant over time, causing time-varying covariate (TVC) effects. In order to overcome this problem, a helpful method is to incorporate stratification on time. This study estimates the survival of chronic renal failure (CRF) patients using the above method. **METHODS:** This analysis was conducted on data from 145 patients in a Malaysian government hospital. The assumption of proportionality was analyzed by using log cumulative hazards curves plotted against log time (log-minus-log) and Schoenfeld residuals and scaled Schoenfeld partial residuals. TVC was analyzed by the interactions of prognostic factors with log time. Violation of the proportionality assumption was overcome by stratification on time of the prognostic factors. **RESULTS:** Median survival time of CRF patients in the study was estimated at 4.5 years. The significant prognostic factors were ex-smokers ($p=0.043$), current smokers ($p=0.035$) and post-renal failure hypertension ($p=0.054$). The proportionality assumption was violated in the ex-smokers' factor as shown by log-minus-log and Schoenfeld residuals and scaled Schoenfeld partial residuals. Stratification on time at 0.8 years was applied to correct the problem. **CONCLUSIONS:** Survival analysis in this study using the Cox proportional hazards model was affected by the TVC effect on the ex-smokers as a prognostic factor. Stratification on time was able to overcome this problem.

RESEARCH ON METHODS - Conceptual Papers

PRM42

MULTIPLE CRITERIA DECISION ANALYSIS FOR HEALTH TECHNOLOGY ASSESSMENT

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OBJECTIVES: This paper will discuss the different methods of multi criteria decision analysis (MCDA) that could be used in health technology assessment (HTA) and their relative merits.Description: The current practice of health technology appraisals is based on the incremental cost-effectiveness ratio (ICER) i.e. the incremental cost per quality adjusted life year (QALY) gained by recipients of treatment. Even though other factors (e.g. severity, life saving, etc) are considered along with ICERs, there is concern that its approach may fail to capture other important sources of value. **METHODS:** MCDA is aimed at supporting decision makers faced with evaluating alternatives taking into account multiple, and often conflictive, criteria in an explicit manner. An overview of MCDA is provided and is compared against the current health technology appraisal processes. A number of important questions are addressed to identify the most appropriate MCDA method that might be used to support decision making. For example, what criteria should be incorporated? Whose weights should be used and how to elicit them? How to incorporate uncertainty into the MCDA process? How do we consider the value of displaced technologies? What should the 'basic' cost-effectiveness threshold be? How do we estimate it? This paper will discuss these questions, outline and assess methodological issues that would be raised by the use of MCDA in health technology assessment (HTA). **RESULTS:** Most of the proposed MCDA approaches in literature use the same technique (weighted sum approach), however, more flexible approaches are available that are relevant to health technology appraisal and value based pricing (VBP). **CONCLUSIONS:** There are general practical issues that might arise from using this MCDA approach in the HTA process and further research needs to be performed to address the issues identified in order to ensure the success of this MCDA technique in the appraisal process.

PRM43

ROLES AND SELECTION OF COMPARATIVE TREATMENT(S) IN THE ASSESSMENT OF NEW DRUG REIMBURSEMENT AND PRICING APPLICATION TO TAIWAN NATIONAL HEALTH INSURANCE (NHI)

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The *Principles on Drug Reimbursement Price Approval*(PDRPA) is the basis for pricing new pharmaceuticals for NHI reimbursement in Taiwan. PDRPA describes the scope of comparative treatments and defines the 3**Categories of new drug as:** 1 (breakthrough); 2A (moderate improvement); and 2B (similar) based on the comparative effectiveness of new drug to the current therapies, which links to the decision of pricing method used. The selection of comparator is crucial in technology assessment and has profound influence on the pricing decision. Hereby we explicitly describe the selection rules and roles of comparator(s). To sort out the rationale of comparator selection, the following 8 features of a comparator are considered: 1) indication(s) approved by department of health Taiwan; 2) associated reimbursement guidance; 3) ATC (Anatomical Therapeutic Chemical) classification; 4) clinical guidance of using the comparator on treating target disease by new drug; 5) comparative evidence such as head-to-head trial or indirect comparison; 6) NHI reimburse price; 7) prices of comparator in the 10 reference countries; and 8) recent utilization in NHI. Clinical relevant and appropriateness are the priority of comparator(s) selection. To be qualified as class 1 or 2A new drug, the currently best therapy should be used as comparator. Then one of the 6 pricing methods will be chosen to decide the reimbursement price of the new drug, with or without reimbursement guidance on using the new drug; and/or the decision to initiate price-volume agreement or (financial) risk sharing negotiation with the pharmaceutical company. Five possible roles of the comparator(s) would play in the assessment: 1) to justify the comparative effectiveness to the new drug; 2) to calculate the price of new drug; 3) to evaluate the net budget impact; 4) as reference setting for reimbursement guidance; and 5) be used in pharmacoeconomic study.

PRM44

CLINICAL AND COMPARATIVE ECONOMIC VALUE - A NOVEL PHARMACOECONOMIC ANALYSIS EMBEDDED IN THE DRUG DEVELOPMENT PROCESS

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OBJECTIVES: Pharmaceutical companies are under pressure to assess the economic value of their pipeline assets. Pharmacoeconomic (PE) analysis can be employed to improve the decision-making process by providing robust estimations of comparative economic value before the commercial launch. Clinical and Comparative Economic Value (CCEV) methodology, has been developed to provide insights into the sources of economic values of innovative products (drugs, devices, services) to inform critical decisions across the product life cycle. **METHODS:** A multi-state disease model is developed to simulate the major clinical events in the dis-

ease progression. Real-world data on actual health care resource consumption and patient clinical characteristics are used. Time horizon of the models should be long enough to capture meaningful differences in outcomes. The differential clinical attributes of the products are identified and direct links are established with the corresponding economic values. The resulting impact on disease progression and consequences for consumption of health care resources are simulated. The primary output is the cost-avoidance against the chosen comparator, with corresponding breakdown by each clinical attribute. **RESULTS:** CCEV directly translates the differences in clinical outcomes to the differences in economic values. This methodology has been effectively applied in the decision process at different stages of drug development, such as, to prioritize pipeline assets by comparing the potential economic value of assets under development and quantifying the value of each differentiated output. These insights are used to guide and design the following data generation strategies. **CONCLUSIONS:** CCEV methodology directly translates clinical outcomes to economic values and is a practical PE tool for decision makers. It can be employed across the entire product life-cycle, starting from the early stages of drug development.

PRM45

ARE MINIMAL CLINICALLY IMPORTANT DIFFERENCE MEASURES (MCIDS) RELEVANT FOR SURVIVAL OUTCOMES? INTRODUCING THE MCID-CAC

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Minimal Clinically Important Difference margins (MCIDs) are being applied by reimbursement agencies to assess the non-inferiority of new medications against comparator medications in the Asia Pacific Region. If a new medication is deemed non-inferior to an all ready reimbursed medication either via direct or indirect comparison methods the newer product is generally reimbursed at the same price as the comparator medication (ie. through cost-minimisation). The concept of an MCID margin for survival outcomes, however, is problematic and controversial. A superficial consideration of MCIDs for survival outcomes may lead to the conclusion that the MCID for survival is inappropriate and no difference in survival is acceptable. As such, the MCID for survival should be zero. In this case such an analysis would become a superiority analysis. If this approach to the assessment of such products were to prevail, new products with a high likelihood of affording patients a survival benefit compared to their comparator products may be rejected even on a cost-minimisation basis. Instead, where the point estimate of treatment effect favours the new treatment serious consideration should be given to reimbursing the new product at the same or higher price. Using indirect comparison methods and real world hazard ratio data this research introduces the concept of MCID-cumulative acceptability curves (MCID-CAC) as an aid to making pragmatic reimbursement decisions for new products that may extend patients lives.

DISEASE-SPECIFIC STUDIES

CANCER-Clinical Outcomes Studies

PCN1

BISPHOSPHONATES AND RISK OF OSTEONECROSIS OF JAW IN CANCER PATIENTS: A META-ANALYSIS

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OBJECTIVES: This meta-analysis aims to assess the potential risk of osteonecrosis of jaw and bisphosphonate use in cancer patients . **METHODS:** The published literature was systematically searched and reviewed using MEDLINE (1950 through July 2011), EMBASE (1980 through July 2011), and the Cochrane Central Register of Controlled Trials (*The Cochrane Library 2011 issue 1*). Studies that included specific risk estimates were pooled using a random-effects model. The bias and quality of these studies were assessed with RevMan statistical software (version 5.0) and the GRADE method of the Cochrane Collaboration. **RESULTS:** A total of 32 publications met inclusion criteria, but only 9 studies that included 51580 subjects for analysis. No randomized controlled clinical trials, meta-analysis or quality of life articles were found that contained data for risks or prevalence of osteonecrosis. The results of a meta-analysis that pooled data from 10 cohort studies indicated that the overall multivariable odds ratio and hazard ratio were 1.11 (95% CI: 0.15, 8.47) and 0.35, 23835 , respectively (95% CI 0.51 to 1.00; p = 1.00), respectively. The risk of osteonecrosis associated with biophosphonate was statistically significant. The results of the quality assessment of these studies indicated low scores using the GRADE method. **CONCLUSIONS:** The uses of bisphosphonates is likely to be associated with the increased risk of osteonecrosis of jaw in cancer patients.

PCN2

THE RELATIONSHIP OF FOLLOWING LIPID-LOWERING DRUGS USED WITH ADJUVANT HORMONAL THERAPY IN BREAST CANCER WOMEN

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OBJECTIVES: Extended adjuvant hormonal therapy with aromatase inhibitors (AIs) or tamoxifen can both effectively reduce the recurrence of breast cancer, but the potential of change lipid profile with AIs compared to tamoxifen was observed in some clinical studies. The aim of this study was to evaluate whether the hormone adjuvant therapy will increase the prescribing rate of lipid-lowering drugs (LLDs) in breast cancer women. **METHODS:** A retrospective cohort study was conducted using the National Health Insurance Research Database between January 1997 and December 2008. The inclusion criteria were adult women who were newly diagnosed with breast cancer and without past history of hyperlipidemia or other cancer diseases between 1998 and 2008. The study endpoint was defined as emerging of the first prescription of LLDs within the exposure period. Adjusted hazard ratio (HR) for the first LLDs prescription was analyzed using multivariable Cox proportional hazards regression model. **RESULTS:** There were 378, 1148 and 756 breast cancer patients treated with AIs, tamoxifen and didn't receive hormonal therapy, respectively. Compared to the non-hormonal therapy cohort, the rate of prescribing LLDs was lower in patients who treated with tamoxifen after adjusted age and comorbidity (HR=0.68, [95% CI=0.46-0.99]), and non-significantly increased in patients who treated with AIs (HR=1.12 [95% CI=0.65-1.91]). In addition, the prescribing LLDs rate between AIs treatment and treatment with tamoxifen was non-significantly increased (HR=1.41 [95% CI=0.83-2.83]) in the head to head comparison. **CONCLUSIONS:** Results from this study indicated that AIs does not significantly increase the risk of prescribing LLDs compare to the patients without hormonal therapy. In contract, the tamoxifen therapy was significantly reduced the prescription rate of LLDs, thus tamoxifen might had potential benefit on lipid metabolism.

PCN3

IMPROVEMENT OF THE 3RD GENERATION COLORECTAL CANCER GENE CHIP

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OBJECTIVES: Colorectal Cancer (CRC) has now become the second leading cause of death in Taiwan, and is one of the cancers with highest incidence in women. Our goal is to integrate comprehensive information to determine the relation between omics and clinical pathology by a systematic biomedical approach and further improve our third generation gene chips for higher sensitivity and specificity toward colorectal cancer. **METHODS:** : One hundred and five patients colorectal cancer patients who had undergone curative surgical resection of colorectal cancer were studied. The copy number for each SNP probe set taken from a tumor sample was calculated by comparing the probe intensity to the reference probe intensity from non-neoplastic tissue, and creating a list of the genome-wide copy number data. **RESULTS:** Among 105 patients with a median follow-up period of 5.6 years (range, 4.1-10.8 years), 23 developed early disease recurrence, whereas 82 did not. Most of them were male and less than 60 years (p=0.044). Stage III, deeper invasive tumor (T3+ T4) and positive lymph node metastasis could be found seriously by 70.5%, 92.4%, and 68.6%, respectively. CEA, EV12B, ATP2A2, S100B, KLK7, TM4SF3, and OLFM4 had copy number gains and high expression levels (P< 0.05) in no recurrence vs. recurrence. **CONCLUSIONS:** Patients less than 60 years were significantly risky to get early relapse in colorectal cancer. In comparison to traditional colorectal cancer gene chip, we would weight higher on EV12B (RR 4.622, 95% CI 1.741-12.270, p=0.001), ATP2A2 (RR 4.688, 95% CI 1.443-15.232, p=0.006), and S100B (RR 11.521, 95% CI 2.688-49.377, p=0.0001).

PCN4

ROLE OF 5-ALPHA-REDUCTASE INHIBITORS, STATINS, ASPIRIN, NSAIDS ON THE DEVELOPMENT OF PROSTATE CANCER IN BENIGN PROSTATIC HYPERPLASIA PATIENTS-A POPULATION BASED STUDY

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OBJECTIVES: The 5-alpha-reductase inhibitors (5-ARIs), statins, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) were previously reported to have protection effect for prostate cancer. The aim of this study was to simultaneously investigate these drug effects on prostate cancer risk among benign prostatic hyperplasia (BPH) patients. **METHODS:** Newly diagnosed BPH patients (ICD-9-CM code: 185 and A-code: A124) with at least one prescription of BPH medications (5-ARIs, alpha-blockers) were identified from Taiwan Longitudinal Health Insurance Database 2000 in 1998-2008. Drug usages of 5-ARIs, statins, aspirin, traditional NSAIDs (tNSAIDs), and cyclooxygenase-2 (COX-2) selective inhibitors were computed in terms of define daily dose (DDD), and were further categorized into high and lose dose groups by medians. The Cox regression was used to estimate hazard ratios (HRs) for the occurrence of prostate cancer. Additional covariates in the model included age, time-dependent covariates of drug usages and Charlson comorbidity score. **RESULTS:** There were 758 prostate cancers indicated from the registry dataset for catastrophic illness patients from 41,955 BPH patients. The analysis of all studied drugs showed significant protection HRs from univariate analyses. After adjusting for covariates, the multivariable analysis showed significant protection effects on high dose of 5-ARIs (HR=0.47, 95%CI= 0.26-0.99), on high dose of statins (HR=0.56, 95%CI= 0.38-0.83), on both low and high dose of tNSAIDs (HR=0.42, 95%CI= 0.36-0.50; HR=0.25, 95%CI= 0.20-0.31), and on both low and high dose of aspirin (HR=0.73, 95%CI= 0.60-0.88; HR=0.34, 95%CI= 0.26-0.45). The COX-2 selective inhibitors became not significant. **CONCLUSIONS:** The 5-ARIs, statins, tNSAIDs, aspirin and COX-2 selective inhibitors have been separately investigated their protection effects on the development of prostate cancer. Our results indicated that the protection effects of 5-ARIs, statins, tNSAIDs and aspirin were independently significant. In addition, the protection effect from COX-2 selective inhibitors was appeared to be confounded by other medication.

PCN5

IMPACT OF ERYTHROPOIESIS STIMULATING AGENTS ON SURVIVAL AMONG PATINETS WITH COLORECTAL CANCER RECEIVING CHEMOTHERAPY

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OBJECTIVES: To evaluate the effect of Erythropoiesis stimulating agents (ESAs) use on survival among colorectal cancer patients undergoing chemotherapy. **METHODS:** This study was a nonconcurrent prospective cohort study using the